

Perspective*Perspective on Gu et al., p. 514***Walking the Walk from Genes through Telomere Maintenance to Cancer Risk**

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Abstract

Recent studies have shown associations between human population single-nucleotide polymorphisms (SNP) and white blood cell telomere shortness; independently, telomere shortness has been associated with higher risks of various cancers. However, no single previous study simultaneously linked a given SNP both with telomere length and reduced risk of cancer. In this issue of the journal (beginning on page 514), Gu and colleagues report four new SNPs associated, in three cohorts, with telomere length. One of these SNPs predicted risk for bladder cancer, an effect partially mediated by telomere length. Interventions that could forestall telomere shortening should be explored for their potential to reduce cancer risks. *Cancer Prev Res*; 4(4); 473–5. ©2011 AACR.

Many factors—genetic, epigenetic, and nongenetic—determine risks for cancers. The relative importance of their contributions is an overarching question. Telomere maintenance provides an interesting case in point in which these considerations rise to the fore. Much interest has focused recently on the significance of telomere shortening, as captured in clinical samples, in relation to a host of disease-associated factors that include risks for aging-related diseases such as cancers (1–5).

Telomeres are the essential regions of DNA at the termini of chromosomes, consisting of tracts of repeated DNA sequences that cap and stabilize the ends of chromosomes (6). If a cell's telomeres become critically short, the cell usually ceases to divide or is subjected to genomic instability. Telomeric DNA falls into a curious category because it uniquely combines genomic and epigenetic-like properties; telomeric DNA, like genes, constitutes a structural part of the genome, yet unlike genes, its sequence does not carry genetic information. Furthermore, the lengths of the telomeric DNA tracts on human chromosomes are changeable throughout life: They are subject to shortening unless they are replenished by telomerase action, which adds telomeric repeats to the chromosome ends by a reverse transcriptase-like mechanism. Indeed, telomeric DNA is highly malleable throughout life, and even from one cell division to another, because it is frequently degraded and then often rebuilt up again, primarily by telomerase. Accordingly, telomeric DNA has "epigenetic-like" properties because it

is changeable throughout life without any change in the genetic information content; yet, unlike classic epigenetic changes, it is a primary DNA sequence (number of repeats in a telomeric tract) itself that changes. Telomeric DNA is thus not easily pigeonholed into conventional definitions of genetic versus nongenetic.

Telomeric DNA itself (which consists of an array of the same short repeated sequence unit tandemly repeated up to thousands of times at each chromosome end) does not encode any protein or known functional gene products, so telomeric DNA is not a gene. Rather, the length of its telomeric DNA repeat tract determines a telomere's functionality. Numerous quantitative relationships have emerged that link shorter tracts of telomeric repeats to cancer and other disease risks [(1–5) telomere length is often, for practical reasons, measured simply as mean telomere length in white blood cells from blood draws]. The components of the telomere-replenishing enzyme telomerase are encoded by normal single-copy genes. Several rare Mendelian genetic mutations in known telomere maintenance genes (telomerase component genes, in most cases) have been studied in humans. Such mutations are known to reduce the activity of telomerase-encoding genes in the mutant-carrying members of the afflicted families and to cause their telomeres to be shorter than those in family control members, and they clearly cause diseases and reduced lifespan (7). Prominent in the spectrum of diseases is the inability to sustain, throughout life, immune system cellular replenishment and replenishment of lung, liver, epidermal, and alimentary tract tissues. Also observed are large increases in the incidence of various cancers (2).

In general population cohorts, some polymorphisms [e.g., single-nucleotide polymorphisms (SNP)] for genes encoding telomerase or telomere components are common enough to have enabled associations to be seen between a SNP and white blood cell telomere shortness (8–10). Independently, multiple population studies have also

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found that blood cell telomere shortness is associated with higher risks, incidence, or mortality of various cancers (1, 2). However, previously no study had linked a common human population SNP simultaneously with both telomere length and, in the same cohort, reduced risk of cancer. In this issue of the journal, Gu and colleagues (11) report 4 new SNPs associated with short white blood cell telomere length. In case-control analyses, the variant allele of one of these SNPs that was associated with longer telomeres, rs398652 on 14q21, also predicted reduced risk for bladder cancer, with an odds ratio of 0.81 (95% CI, 0.67–0.97; $P = 0.025$).

It will be of much interest to understand the role(s) of the gene(s) affected by these SNPs. As has often been pointed out, genome-wide associations have the great value for cancer research of both providing an objective assessment of mechanisms that promote cancer in humans and for discovery or validation of new pathways. Thus, importantly, a mechanism that may not have been considered previously can be brought to light by genome-wide association study (GWAS) approaches. The 14q21 SNP is 60 kb from a gene encoding pellino-2 protein. The family of 3 pellino proteins has E3 ubiquitin ligase activity and plays important roles in innate immune response and inflammation (12). The SNP is also located in a region shown to have a high linkage with telomere length in a previous genetic linkage analysis (13).

An important question raised by all the studies associating a genetic (or nongenetic) variable with telomere length, and associating telomere length with altered disease risk, is whether the (genetic or nongenetic) variable being studied changes the disease risk because of its effect on telomere length, or whether the variable both causes telomeres to be longer and, independently, causes the observed change in risk, or some combination of the two. This question is answered in the present article by Gu and colleagues. In a mediation analysis testing the interrelationships among the SNP, telomere length, and cancer protection, the authors found that telomere length was a significant mediator of the relationship between rs398652 and bladder cancer ($P = 0.013$), explaining 14% of the cancer-protective effect. This mediation result is similar in kind to other mediation analyses, including studies by this group (14), showing significant indirect (or partial) effects of a genetic variant on cancer risk. The notable conclusion here is that the 14q21 SNP is protective against bladder cancer risk both because of and independently of its positive effect on telomere length.

Another important question is how to interpret the finding that the 3 other SNPs (at 1p34.2, 6q22.1, and 20q11.22) that were associated with longer white blood cell telomeres were not significantly associated with lower risks for bladder cancer. Are telomere longness and lower cancer risk separable? It seems not. In the case of the only SNP associated with both telomere length and bladder cancer risk, the risk was mediated in part by telomere length. Therefore, are the 3 nonrisk SNPs simply associated with a milder effect on telomere length? This, too, does not

seem likely. The GWAS of SNP–telomere length associations found a similar magnitude of association with telomere length for all 4 SNPs. Indeed, SNPs explain only small variation in telomere length, and telomere length explains only small variation in bladder cancer risk. Therefore, it is reasonable to infer that because the other 3 SNPs do not reduce bladder cancer risk, they must not have a beneficial influence on the non-telomere-related factors that contributed to reduced bladder cancer risk with the 14q21 SNP. Left open for further investigation is whether these 3 SNPs reduce the risk of other cancers or diseases in a manner mediated by telomere length.

Nongenetic, as well as genetic, influences on both telomere length and disease risks have also emerged in studies in humans. In various cohorts, white blood cell telomere shortness has been associated with factors falling under the general umbrella of psychological stress, as captured by measures such as perceived stress, situations of stress (e.g., prolonged caregiving for a disabled family member or childhood adversity), eating disorder patterns associated with stress, and measures of personality traits (e.g., pessimism and hostility), as well as socioeconomic factors such as low educational level (15, 16). In turn, many of these measures themselves have also been linked—but again, mostly in separate studies—to risks of diseases including cardiovascular disease, reduced immune functions, and diabetes (to date, however, comparable data for cancer have been much more limited). On the plus side, exercise has been observationally linked both to longer telomeres and to reduced risks for some common diseases of aging, including cancer (17). However, again, these studies generally have not established whether the exercise was directly or causally linked via telomere length to the reduced disease risks observed.

The findings on nongenetic influences on telomere length and disease risk prompt the same question raised above: To what degree are these nongenetic influences on disease risk mediated via their effects on telomere length maintenance? Regardless of the answer, the results to date on nongenetic influences on both telomere shortness and risks for other diseases should prompt further research into whether comparable nongenetic influences exist for cancers, and if so, by what mechanism(s).

The study by Gu and colleagues (11) also shows a joint effect between the risk genotype of rs398652 and smoking in elevating the risk of bladder cancer, which is tobacco-related. They compared, either in never-smokers or in ever-smokers, the protective genotypes versus the risk genotype. Ever-smokers with the risk genotype had the highest risk of bladder cancer. Even though the protective form of the 14q21 SNP associated with longer telomeres significantly lowered the risk of bladder cancer in the combined group of never- and ever-smokers, its beneficial effect was driven by the effect in never-smokers. Although for this cancer tobacco exposure still exerted the quantitatively larger effect on risk, the broader question of great interest is whether nonalterable genomic factors (SNPs such as those reported by Gu and colleagues) synergize with potentially malleable

nongenetic influences (e.g., lifestyle, behavioral, stress, and environmental factors). A recent study in aged telomerase-deficient mice showed that telomere reactivation through knock-in of an inducible telomerase component (*TERT*) gene resulted in a marked reversal of their phenotypes of degenerative disease, suggesting that restoring telomere integrity may have clinical implications for preventing aging-related diseases (18). Whether interventions or behavioral changes in humans that could lengthen telomeres (or at least forestall their shortening) might influence cancer risks is not yet known. Given the vast numbers of people nationally and worldwide who are at eventual risk of progressing to advanced cancers, such approaches could add up to a significant lessening of the population burden of cancer and should therefore be explored.

The large body of remarkable cancer research in the past few decades directed toward understanding and treating advanced cancers has also had a significant ripple effect; it has shed light on the biology of early cancers and their initiating events. These advances now create unprecedented

opportunities for novel approaches directed at prevention and early interception of cancer's deadly trajectory (19). Although treating or even curing cancer is often at the forefront of people's minds, cancer will never be brought under control unless the other side of the equation is addressed: preventing it. This is not impossible. Just from smoking control efforts alone, countless cancers have been prevented. Prevention is clearly more cost-effective—counting both human and material costs—than treatment. The resources that will not otherwise have to be used for treating preventable cancers can be freed up for treating cancers, at all stages, with the rapidly growing armamentarium of emerging therapies.

Disclosure of Potential Conflicts of Interest

The author is a co-founder of Telome Health, Inc.

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